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<b>(21) International Application Number:</b> PCT/EP97/01560 <b>(22) International Filing Date:</b> 25 March 1997 (25.03.97) <b>(30) Priority Data:</b> 9606677.4 29 March 1996 (29.03.96) GB <b>(71) Applicant (for all designated States except US):</b> GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> VAN OORT, Michiel [CA/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). SACCHETTI, Mark, J. [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). <b>(74) Agent:</b> DAWSON, Hugh, B.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PROCESS AND DEVICE FOR INHALATION OF PARTICULATE MEDICAMENTS  <b>(57) Abstract</b>  A process for dispersing medicament from an inhalator device which contains medicament particles. The process involves (i) providing an inhalator which contains at least one dose of medicament particles comprising spherical hollow particulates of respirable particle size suitable for deposition in a human being's lungs, and (ii) removing the spherical hollow particulates from the inhalator.		

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## PROCESS AND DEVICE FOR INHALATION OF PARTICULATE MEDICAMENTS

Field of the Invention

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The present invention relates, in general, to particulate medicaments and dosing of the medicaments for inhalation by a patient. More specifically, the present invention relates to a particulate medicament and a method for dosing of the medicament, wherein the medicament is in the form of spherical hollow particulates.

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Background of the Invention

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Asthma and other respiratory diseases are typically treated by the inhalation of an appropriate medicament for deposition into the lungs of a human to ease patient breathing and increase air capacity. Two treatments for respiratory diseases have been widely used. One is inhalation of a medicament from a drug solution or suspension, typically in an aerosol container (i.e., a pressurized container such as a metered dose inhalator) that has a spray valve and uses a gas propellant. The second is inhalation of a powdered drug (generally admixed with an excipient) from a dry powder inhalator.

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Manufacture of pressurized aerosol containers filled with medicament and useful as inhalators for respiratory drug delivery is well known, and a representative discussion of such manufacture can be found in Byron, P., Respiratory Drug Delivery, CRC Press, Inc. 185 et seq., (1990) In connection with the manufacture of aerosol inhalators, it is noted that in view of recent evidence of the link between chlorofluorocarbon gas emissions and the deterioration of the earth's protective ozone layer, use of drugs in pressurized aerosol inhalators employing a chlorofluorocarbon (i.e., materials that are totally halogenated

with both chlorine and fluorine and thus have no hydrogen on the carbon, for instance, trichloromonofluoromethane, sold by DuPont under the registered trademark FREON 11 and colloquially known as CFC-11, or dichlorodifluoromethane, sold by DuPont under the registered trademark FREON 12 and colloquially known as CFC-12) as the gas propellant  
5 has declined. Each of FREON 11 and FREON 12 has an ozone depletion potential (hereinafter, ODP) of 1, and the Environmental Protection Agency of the U.S. Government has imposed regulations to phase out use of such propellants having an ODP = 1.

Instead, environmentally safe propellants having an ODP  $\geq 0$  and  $< 0.5$  are of increasing  
10 interest for use in pressurized aerosol inhalators. Examples of such environmentally safe propellants include, but are not limited to, the following: monochlorodifluoromethane (a hydrochlorofluorocarbon which has an ODP = 0.05 and is sold by DuPont under the registered trademark DYMEL 22); perfluoroethane; 1,1,1,2-tetrafluoroethane (which has an ODP = 0 and is sold by ICI under the trade name HFC-134a); and 1,1,-difluoroethane  
15 (which has an ODP = 0 and is sold by various companies under the trade name HFC-152a).

Also, interest in dry powder inhalation systems has increased. Various dry powder inhalator devices for dosing of particulate powdered medicaments to a patient's  
20 respiratory tract employ capsules, blisters, velvet fibers, screens, and the like, as a carrier loaded with powdered medicament. For loading the powder in the carrier for the dosing of the powder via an inhalator, typically a selected amount of the powder (such as 50  $\mu\text{g}$ ) is admixed with a suspending agent (such as perfluoro-pentane), and the resultant suspension is then dispensed from a metering device to the carrier, after which the  
25 suspending agent evaporates and leaves micronized dry powder particles on the carrier.

During use of the inhalator, an air stream (either generated by the patient or by an assist device, as is well known in the art) lifts the powder from the carrier to entrain the powder within the air stream which is then inhaled by the patient. The dose of a powder type of medicament employed with such dry powder inhalator devices is, in most instances, significantly less than 50 mg, typically less than 5 mg, and usually about 50 to about 500  $\mu$ g. The powdered particles contained in the inhalator are micronized, solid particles, typically having an average particle diameter (colloquially referred to as particle size) of  $< 10 \mu$ m, more particularly  $< 6 \mu$ m, even more particularly  $< 5 \mu$ m, which is an appropriate size so that the particles can be drawn into the lungs.

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Representative dry powder inhalator devices having medicament carriers therein and suitable for dispersing of respirable medicaments to patients are disclosed in U.S. Patent Nos. 3,906,950, 4,013,075, 3,807,400, and 3,991,761, each to Coccozza; U.S. Patent No. 4,161,516 to Bell; U.S. Patent No. 4,395,421 to Taylor et al.; European Published Patent Application No. 0 455 463 A1 to Velasquez et al.; European Published Patent Application No. 0 211 595 A2 to Newell et al.; European Published Patent Application No. 0 4670 172 A1 to Coccozza et al.; PCT International Publication No. WO 92/00115, published January 9, 1992, to Gupte et al.; and PCT International Publication No. WO 94/20164, published September 15, 1994, to Mulhauser et al. Also, the commercially available TURBUHALER® inhalator is disclosed in U.S. Patent Nos. 4,667,668 and 4,805,811, each to Wetterlin, and U.S. Patent No. 4,668,218 to Virtanen. The disclosures of all of these are incorporated herein by reference.

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Additionally, it is noted that U.S. Patent No. 5,503,869, issued April 2, 1996, and US Patent Application Serial No. 08/328,578, filed on October 21, 1994, both to Van Oort, the disclosures of which are incorporated herein by reference, describe a medicament

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carrier which is adapted for use in a dry powder inhalator device and includes at least one carrier screen having carrier surfaces that define a plurality of interstices in the screen. At least one dose of a powdered medicament is loaded onto the carrier screen surfaces whereby the interstices of the screen are at least partially open and free of the powdered medicament. Spray drying for preparation of particles, including for selected medicinal uses, is well known. Additionally, the concept is well known that, under certain conditions during spray drying from solution, the resultant particles are not solid, but rather are hollow structures. Selected uses of such hollow structures involve certain medical applications.

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For instance, U.S. Patent 4,590,206 to Forrester et al. shows spray dried respirable medicament particulates, such as sodium cromoglycate, in the shape of doughnut rings, where the hollowness is the hole in the middle of the ring and the ring is solid. Since spray dried hollow spheres have a low particle density, they are considered by Forrester et al. to be too fragile and are consequently to be avoided.

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Also, U.S. Patent No. 4,127,622 to Watanabe et al. shows hollow particulates for gastric medicines suspendable in gastric juice and which may remain in the stomach for a long time. They are prepared by dissolving S-PI (substance for pepsin inhibition as the active ingredient) and ethylcellulose (as the excipient) in a lower chlorinated hydrocarbon (as the solvent), so that the concentration of ethylcellulose is 0.5 to 4% by weight on the basis of the total weight of the solution, and then spray drying the solution at a temperature higher than 50°C.

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Also, of interest in connection with hollow structures for useful as medicaments is the disclosure of PCT International Publication No. WO 91/12823, published September 5,

1991, to Illum et al. This publication describes hollow (i.e., gas-filled or vapor-filled) microcapsules (for instance, albumin) prepared by forming a shell around a solid or liquid core (for instance the volatile oil, perfluorohexane), and then removing the core. The shell may be made by variations on spray drying, such as simple or complex coacervation, oil/water/oil double emulsion, or MSIEP (minimization of solubility at isoelectric point) methods, followed by chemical or heat hardening to render the shell water insoluble. The double emulsion method results in each microcapsule having a honeycomb appearance with multiple gas-filled chambers. The microcapsules are injected into the blood of a human for use in echocardiography.

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Nevertheless, such spray drying techniques to achieve spherical hollow particulate structures for respirable medicaments that are to be inhaled by the patient have not previously been employed.

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#### Summary and Objects of the Invention

Accordingly, the present invention provides a process for dispersing spherical hollow medicament particulates from an inhalator device. The inhalator device may be a dry powder inhalator having contained therein a medicament carrier loaded with at least one dose of dry powdered medicament particles comprising spherical hollow particulates of respirable particle size suitable for deposition in a human being's lungs. Alternatively, the inhalator device may be a pressurized aerosol inhalator, such as a metered dose inhalator, having contained therein a propellant and at least one dose of medicament particles comprising spherical hollow particulates of respirable particle size suitable for deposition in a human being's lungs. For both dispersion from the dry powdered inhalator and from the pressurized aerosol inhalator, the spherical hollow medicament particulates should

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have a mass median aerodynamic diameter suitable for deposition in a human being's lungs.

5 Additionally, the present invention provides an inhalator device suitable for dispersing medicament therefrom and containing medicament therein, where the medicament comprises spherical hollow particulates that are of respirable particle size. The inhalator device may be a dry powder inhalator. Alternatively, the inhalator device may be a pressurized aerosol inhalator, such as a metered dose inhalator. For both the dry powdered inhalator and the pressurized aerosol inhalator, the spherical hollow  
10 medicament particulates should have a mass median aerodynamic diameter suitable for deposition in a human being's lungs.

It is therefore an object of the present invention to provide a medicament for use in an inhalator which provides for administration of a dosage of medicament particles wherein  
15 the particles that leave the inhalator and are inhaled into the patient's lungs are formed as spherical hollow particulates having a desirable aerodynamic particle size and thus are of respirable particles size (i.e., they should have a mass median aerodynamic diameter suitable for deposition in a human being's lungs) for maximum beneficial efficiency, providing maximum efficacy to the patient.

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It is an advantage of the present invention that the spherical hollow particulate form can improve the deaggregation properties of the medicament for entrainment in the stream, as the medicament is moving from the inhalator device into the patient's lungs, since the spherical hollow particulates can be made with a large geometric diameter and thus will  
25 have less surface-to-surface contact with each other as compared to conventional micronized solid particulates that have a relatively smaller geometric diameter.



Some of the objects and advantages of the invention being stated, other objects will become evident as the description proceeds, when taken in connection with the accompanying Figures and Laboratory Examples described below.

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### Brief Description of the Figures

Figure 1 is a photomicrograph of spray dried dimpled solid particulates of the asthma medicament, albuterol sulfate;

10 Figure 2 is another photomicrograph of spray dried dimpled solid particulates of albuterol sulfate:

Figure 3 is a photomicrograph of spray dried spherical hollow particulates of the asthma medicament, amiloride HCl;

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Figure 4 is another photomicrograph of spray dried spherical hollow particulates of amiloride HCl;

Figure 5.13 is another photomicrograph of spray dried spherical hollow particulates of amiloride HCl;

Figure 6 is a photomicrograph of spray dried spherical hollow particulates of the excipient, lactose; and

25 Figure 7 is another photomicrograph of spray dried spherical hollow particulates of lactose.

Detailed Description of the Invention

It is well known that, during inhalation therapy or systemic absorption via the respiratory tract, the human lung separates particles based on the aerodynamic diameter, which is a function of the actual average particle diameter (i.e., the geometric diameter), as well as the shape and the density of the particle. More specifically, a lower particle density will produce a smaller aerodynamic diameter for particles of equivalent geometric size, as illustrated by equation 1 as follows:

$$D_{ae} = D_{geo} p^{1/2} \quad (\text{equation 1})$$

where  $D_{ae}$  and  $D_{geo}$  are the aerodynamic and geometric diameters, respectively, and  $p$  is the particle density.

Because of the spherical particulates being hollow, they have an actual density lower than that of the solid particulates currently employed for respirable medicaments. Thus, applicants have unexpectedly discovered that the spherical hollow particulates should be perceived by the lung as being of a smaller aerodynamic size than the aerodynamic size of the solid particulates of substantially the same actual average particle diameter, and thus the spherical hollow particulates should be deposited deeper in the lungs.

Moreover, the spherical hollow particulates can be made with an actual average particle diameter (i.e., the geometric diameter) greater than that of the solid particulates currently employed for respirable medicaments. In that event, the spherical hollow particulate form would likely improve the deaggregation properties of the medicament for entrainment in the inhalation stream, as the medicament is moving from an inhalator

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device into the patient's lungs, due to the large spherical hollow particulates having less surface-to-surface contact with each other as compared to the relatively smaller solid particulates. As a result, an increase in the respirable fraction of a medicament formulation should be achieved with large spherical hollow particulates as compared to small solid particles, where the mass median aerodynamic diameter of the two is approximately the same.

As noted above, methods for spray drying of particles are well known, and it is also well known that controlling selected conditions for spray drying, such as the temperature, the type of solvent, the concentration of the active ingredient and/or the optional excipient, can result in the spray dried particles being hollow structures instead of solid. Any of the various well known spray drying methods may be employed for spray drying the medicament particles in accordance with the present invention to form spherical hollow structures useful for inhalation therapy or systemic absorption via the respiratory tract, including those spray drying methods disclosed in the above-mentioned U.S. Patent 4,590,206 to Forrester et al., U.S. Patent No. 4,127,622 to Watanabe et al. and PCT International Publication No. WO 91/12823 to Illum et al., the disclosures of which are incorporated herein by reference.

Various solvents may be employed during spray drying, including, but not limited to, hydrocarbons, halogenated hydrocarbons (i.e., fluorinated hydrocarbons or chlorinated hydrocarbons), alcohols, ketones, and the like. Examples of suitable solvents include, but are not limited to, water, hexane, perfluoromethylcyclohexane, perfluorohexane, perfluoropentane, dichloromethane, ethanol, acetone, and combinations thereof.

Medicament particles which may be spray dried in accordance with the present invention to form spherical hollow particulates are suitable for use as respirable medicaments for inhalation therapy or systemic absorption via the respiratory tract to treat respiratory disorders such as asthma, bronchitis, chronic obstructive pulmonary diseases and chest infection. Additional medicaments may be selected from any other suitable drug useful in inhalation therapy and which may be presented as a suspension or in a dry powder inhalator. Appropriate medicaments may thus be selected from, for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; anti-infectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene anti-inflammatories, e.g. fluticasone, flunisolide, budesonide, tiotropium or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. salmeterol, salbutamol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol or albuterol, or (-)-4-amino-3,5-dichloro- $\alpha$ -[[(6-[2-(2-pyridinyl)ethoxy]-hexyl)amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics, e.g. ipratropium, atropine, oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament. Preferred medicaments are salbutamol, salmeterol,

fluticasone propionate, beclomethasone dipropionate, terbutaline, cromoglycate, budesonide, and triamcinolone acetonide and/or salts thereof.

Moreover, the medicaments optionally may be together with excipients acceptable for inhalation into the human body, which may be organic excipients, such as polysaccharides (i.e., starch, cellulose, and the like), lactose, glucose, mannitol, amino acids, and maltodextrins, or may be inorganic excipients, such as calcium carbonate and sodium chloride. The excipient may be included with the medicament via well known methods, such as by admixing, co-precipitating, and the like.

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When entrained in an inhalation stream for inhalation by the patient, the spherical hollow particulates typically should acquire a mass median aerodynamic diameter, particularly from about 0.5  $\mu\text{m}$  to about 7.0  $\mu\text{m}$ , more particularly from about 1  $\mu\text{m}$  to about 4.5  $\mu\text{m}$ , as perceived by the patient's lungs as the spherical hollow particulates pass into the lungs. Also, the spherical hollow particulates typically should have > 50% of the mass of hollow particulates, more particularly > 70% of the mass of hollow particulates, particularly having a mass median aerodynamic diameter < 6  $\mu\text{m}$ , more particularly < 5  $\mu\text{m}$ , as perceived by the patient's lungs as the spherical hollow particulates pass into lungs. As noted in the above discussion of prior art inhalators, it is particularly useful that particles of respirable particle size range have more than 50% thereof with a mass median aerodynamic diameter < 6  $\mu\text{m}$ , more particularly < 5  $\mu\text{m}$ , for appropriate deposition into the lungs, which should be achieved with the present invention.

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The ability to control the geometric density of the substantially spherical hollow particulates offers an additional advantage over current inhalator systems which use a suspension of medicament particulates in a propellant. In existing systems containing

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drug and propellant suspensions, the suspension may separate or stratify because of the differences in the densities of the medicament and propellant.

5 Separation may be either classified as "creaming" wherein the medicament rises to the top of the more dense propellant, or "sedimentation" wherein the medicament settles to the bottom of the less dense propellant. Regardless of the classification, separation of the medicament and component may cause a lack of dosage uniformity per activation, i.e., each dose may not provide an equal amount of drug over the life of a multi-dose inhalator. The uniformity of dosages delivered by multi-dose inhalators is of critical importance to the efficacy of the device and must be within narrow parameters to meet regulatory  
10 criteria.

The problem of separation of the suspension is generally addressed by vigorously shaking the inhalator immediately before it is used. However, patient compliance with this  
15 simple task is difficult to control and even slight delays between shaking and use effect dosage uniformity.

The present invention, however, overcomes the problem of separation and, in so doing, conceivably eliminates the need to shake the inhalator before use. By allowing the drug  
20 to be density matched to the selected propellant, the tendency of the medicament and propellant to stratify is removed. The drug and propellant are uniformly distributed in suspension and it can be assumed that each dose would then also be similarly uniform.

Medicament density may be pre-selected and controlled by adjusting the spray drying  
25 conditions under which the particulates are created, as previously mentioned. In particular, though, density may be controlled by adjusting the thickness of the walls of



the spheres as compared to sphere diameter, and by adjusting the ratio of drug to excipient when creating composite medicament particulates. In some embodiments, however, it may be preferred to use pure medicaments without excipients. In short, the ability to pre-select and control the geometric density of the medicament particulates offers a significant advantage over existing medicament/propellant suspension systems.

With respect to dry powder inhalators, the spherical hollow particulates of the present invention are suitable for use in any carrier in any dry powder inhalator, including, but not limited to, any of the dry powder inhalators disclosed in the above-mentioned patents and published patent applications.

The spherical hollow particulates of the present invention are also suitable for use in any metered dose inhalator, including the pressurized aerosolized type (where the particulates are together with a propellant and an optional suspending agent). With respect to pressurized aerosol metered dose inhalators, as such pressurized aerosol containers are well known in the art, the spherical hollow particulates may be placed in a pressurized container with a suitable propellant, and optionally with a suitable suspending agent (also known as a dispersing agent or a surfactant) by any of the well known methods therefor, such as that shown in the above-noted Respiratory Drug Delivery, p. 185 et seq. In general, adding a medicament to a pressurized aerosol container is accomplished as follows.

Medicament is added to a high shear blender (i.e., mixer) which contains propellant and may also contain a suspending agent. It may also be preferred to add a polar substance to increase solubility of surfactant in a propellant, e.g. ethanol.

Propellants may be of the chlorofluorocarbon variety (i.e., trichloromonofluoromethane, sold by DuPont under the registered trademark FREON 11 and colloquially known as CFC-11, or dichlorodifluoromethane, sold by DuPont under the registered trademark FREON 12 and colloquially known as CFC-12), which, as mentioned above, are being phased out  
5 by the Environmental Protection Agency of the U.S. Government as each of FREON 11 and FREON 12 has an ODP = 0. Alternatively, propellants may be of the more recently developed environmentally safe varieties. Suitable environmentally safe propellants include, but are not limited to, any of the above-mentioned perfluoroethane, monochlorodifluoromethane, 1,1,1,2-tetrafluoroethane, 1,1,-difluoroethane,  
10 1,1,1,2,3,3,3-heptafluoro-n-propane, and combinations thereof.

Suitable optional suspending agents include, but are not limited to, oleic acid, SPAN ® 85 (registered trademark for the partial esters of the common fatty acids (lauric, palmitic, stearic, and oleic) and hexitol anhydrides (hexitans and hexides), that are derived from  
15 sorbitol and that tend to be oil-soluble and dispersible or insoluble in water}, lecithin, and combinations thereof.

If the propellant has a low boiling point so that it would volatilize during procedures at or near room temperature, then the mixer needs to be maintained well below room  
20 temperature to prevent evaporation or alternatively a sealed mixer (one in a closed system with the container) may be employed. Once a homogenous suspension is obtained, the suspension is filled into aerosol containers. During the filling, the mixer can be used to maintain adequate suspension throughout the entire filling circuit by continuously circulating the suspension through the concentrated filling unit.

At this point, there exist two main options. With the first option, especially for products not using the environmentally unsafe propellant, CFC-11, the entire formulation is prepared in a low temperature pressure vessel and then filled through the valve into evacuated, previously crimped containers. Care must be taken with propellants such as HFC-134a, that have a high vapor pressure, as filling through the valve of the container is difficult with such propellants. The second option involves the manufacture of a lower volatility concentrate. With this alternative technique, filling is in a controlled environment into containers, after which the valves are crimped in place. Subsequently, the high pressure propellant is added through the valve.

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The tensile strength of the spherical hollow particulates will vary depending on the particular medicament (and optional excipient) being spray dried. In the event that the spherical hollow particulates have a weak enough tensile strength so that a large storage container of them, such as a kilogram quantity, would result in upper hollow particulates crushing lower hollow particulates in the container prior to deposition of the hollow particulates in an inhalator device, then formation of hollow particulates should be accomplished in-line so that the formed hollow particulates can be deposited directly after formation into an inhalator device.

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## 20 Laboratory Examples

### Example I

#### Production of hollow particulates by spray drying.

25 Medicament powder of each of the two medicaments, albuterol sulfate and amiloride HCl (abbreviated herein as Alb S and Amil HCl, respectively), is employed in this example.

Also, the excipient, lactose, is employed in this example. Aliquots of each of the medicaments, and also of lactose, are spray dried as follows.

15 g of Alb S (lot no. W 1946 FB) are dissolved in 300 ml of water to create a 5% solution. Similarly, 3.479 g of Amil HCl (lot no. 9007H 902) are diluted in water to 1000 ml to create a solution. Likewise, 15 g of lactose (lot no. 1NC25, 605 from Sheffield Products of Norwich, New York) are diluted in water to 150 ml to create a solution.

Each solution is respectively spray dried using a VIRTIS™ (a spray dryer commercially available from The Virtis Company of Gardiner, New York) with each of the air from the nozzle and from the blower set at its respective maximum value under the following conditions of temperature and rate, as summarized in Table A below:

TABLE A

Spray Dried Particles	Inlet Temp (°C)	Outlet Temp (°C)	Flow Rate Setting (ml/minute)
Alb S (medicament)	150	101	7
Amil HCl (medicament)	150	92	12
lactose (excipient)	180	127	5

Spray drying produced the following average particle diameters (i.e., the geometric diameters) as summarized in Table B below:

TABLE B

5	Spray Dried	Geometric	Hollow
	<u>Particles</u>	<u>Diameter</u>	<u>or Solid</u>
	Alb S	1 to 5 $\mu\text{m}$	dimpled solids
	Amil HCl	1 to 5 $\mu\text{m}$	hollow spheres
	Lactose	2 $\mu\text{m}$	hollow spheres

10 As noted in Table B and as can be seen in the photomicrographs in Figures 1 and 2, spray drying the Alb S produced dimpled solid structures and did not produce spherical hollow particulates. On the other hand, spray drying the Amil HCl produced spherical hollow particulates, as can be seen in the photomicrographs in Figures 3-5. Spray drying the lactose produced spherical hollow particulates, with the largest lactose particulate having  
 15 an average particle diameter of about 17  $\mu\text{m}$ , as can be seen in the photomicrographs in Figures 6 and 7.

While it is not intended to be bound to any theory, it is believed that the concentration of Alb S in water, namely a 5% solution of 15 g in 300 ml, was not low enough for the  
 20 spray drying to result in spherical hollow particulates of Alb S, and thus, lowering the concentration of Alb S should result in spherical hollow particulates. Also, it is believed that admixing the Alb S with an excipient, such as lactose, during the spray drying should result in spherical hollow particulates.

25

#### Example II

Use of hollow particulates in dry powder inhalators.

The following is a discussion of how a DISKHALER™ (a medicament dispersing device, i.e., an inhalator, commercially available from GlaxoWellcome, Inc.) and an AEROBREATHER™ (available from API of Hadley, Massachusetts) may be employed with the spherical hollow medicament particulates of the present invention, such as the Amil HCl made in Example 1, to determine how the powdered medicament is dispersed and thus illustrate that the spherical hollow medicament particulates are useful in a dry powder inhalator. More particularly, the extent to which a medicament is dispersed may be measured by its mass median aerodynamic diameter (MMAD) in micrometers, and the percentage that is less than 6 micrometers, particularly less than 5 micrometers, is indicative of desirable particle size for inhalation into the lungs.

Several DISKHALER™ devices should be employed. The DISKHALER™ has a screen which serves to direct an air jet, thus helping to entrain the particles in the air jet. The 4-blister compartment would be removed from the holder portion of each DISKHALER™.

A dosage of each of the spray dried spherical hollow particulates would be respectively loaded onto the bottom of the holder portion of a DISKHALER™, the bottom serving as a carrier surface. Next, each DISKHALER™ with its respective medicament would be attached to an AEROBREATHER™ for dispersion of the medicament from the carrier. The AEROBREATHER™ is a device that simulates inspiration by a human through the mouth at 60 liters/minute, with an acceleration of 19 liters/second<sup>2</sup> and a total volume of 1 liter.

The inspired powder (which would be approximately 1 milligram) then would be drawn into the AEROSIZER™ unit for aerodynamic particle size analysis. The photomultiplier tubes of the AEROSIZER™ would be operated at 1100 volts, and the data would be analyzed in an auto-combine mode with software version 5.02.37 available from API of

Hadley, Massachusetts. As noted above, the extent to which the powder is dispersed is measured by the MMAD in micrometers, and the percentage that is less than 6 micrometers, particularly less than 5 micrometers, is indicative of desirable particle size for inhalation into the lungs.

5

The results for the dispersed spray dried spherical hollow medicament particulates should be a MMAD from about 0.5 to about 7  $\mu\text{m}$ , particularly about 1 to about 4.5  $\mu\text{m}$ , and a % mass < 6 $\mu\text{m}$  of about 30% or more, particularly about 50% or more, and most particularly about 70% or more. Also, the spherical hollow particulates of the present invention should be deposited deeper in the lungs than are conventional micronized solid particulates (with substantially the same geometric diameter) from a dry powder inhalator.

10

### Example III

#### 15 Use of hollow particulates in pressurized aerosol metered dose inhalators.

The following is a discussion of how an inhalator that is a pressurized aerosol container with a valve may be employed with the spherical hollow medicament particulates of the present invention, such as the Amil HCl made in Example I.

20 Example formulations suitable for a metered dose inhalator according to this invention include (i) a suspension consisting essentially of spherical hollow medicament particulates of respirable size and 1,1,1,2-tetrafluoroethane; and (ii) a suspension of spherical hollow medicament particulates of respirable size, 1,1,1,2-tetrafluoroethane, oleic acid and sufficient ethanol to solubilize the oleic acid.

The spherical hollow medicament particulates should be added to a high shear blender (i.e., mixer) which contains, for instance, 1,1,1,2-tetrafluoroethane propellant (colloquially known under the trade name, HFC-134a) and lecithin suspending agent.

5        However, the vapor pressure of 1,1,1,2-tetrafluoro-ethane propellant at 68°F is 68.4 psig, and hence, the vapor pressure is too great to meet the U.S. Government Department of Transportation requirements for use in aerosol containers when the containers are transported and temperatures can go up to 130°F. Thus, a vapor pressure depressant, such as a glycol ether (i.e., 2-butoxyethanol) or an alkyl acetate (i.e., butyl acetate) should  
10       be used together with 1,1,1,2-tetrafluoroethane propellant so that the resultant suspension in the aerosol container meets the Department of Transportation requirements and has a vapor pressure of less than 180 psig at 130°F.

Also, since 1,1,1,2-tetrafluoroethane propellant has a low boiling point of -15.5°F (-  
15       26.5°C) so that it would volatilize during procedures at or near room temperature, then the mixer should be maintained well below room temperature to prevent evaporation. Alternatively, a sealed mixer (one in a closed system with the container) may be employed.

20       Once a homogenous suspension is obtained, it is filled into aerosol containers. During the filling, the mixer can be used to maintain adequate suspension throughout the entire filling circuit by continuously circulating the suspension through the concentrated filling unit.

25       Because, as noted, 1,1,1,2-tetrafluoroethane propellant has a high vapor pressure, care must be taken during filling as filling through the valve of the container is difficult with



such high pressure propellants. With one technique, the entire formulation is prepared in a low temperature pressure vessel and then filled through the valve into evacuated, previously crimped containers.

- 5 With an alternative technique, the propellant is not placed in suspension with the medicament and suspending agent prior to filling. Rather, filling of the suspension of medicament and suspending agent into each container is accomplished in a controlled environment, after which the valve is crimped in place onto the containers. Subsequently, the high pressure 1,1,1,2-tetrafluoroethane propellant is added through the valve.

10

As noted above, the extent to which a medicament is dispersed may be measured by its mass median aerodynamic diameter (MMAD) in micrometers, and the percentage that is less than 6 micrometers, particularly less than 5 micrometers, is indicative of desirable particle size for inhalation into the lungs.

15

- Accordingly, like the results noted above in Example II for the spray dried spherical hollow medicament particulates dispersed from a dry powder inhalator, the results for the spray dried spherical hollow medicament particulates dispersed from pressurized aerosol containers should be a MMAD from about 0.5 to about 7  $\mu\text{m}$ , particularly about 1 to about 4.5  $\mu\text{m}$ , and a % mass < 6 $\mu\text{m}$  of about 30% or more, particularly about 50% or more, and most particularly about 70% or more. Also, the spherical hollow particulates of the present invention should be deposited deeper in the lungs than are conventional micronized solid particulates (with substantially the same geometric diameter) from an aerosol inhalator.

25

It will be understood that various details of the invention may be changed without departing from the scope of the invention. Furthermore, the foregoing description is for the purpose of illustration only, and not for the purpose of limitation -- the invention being defined by the claims.

CLAIMS

What is claimed is:

- 5 1. A process for dispersing medicament from an inhalator device, the inhalator being adapted for containing at least one dose of medicament, said process comprising:
  - (a) providing an inhalator which contains at least one dose of medicament comprising spherical hollow medicament particulates of respirable particle size suitable for deposition in a human being's lungs, and
  - 10 (b) activating the inhalator to cause the spherical hollow medicament particulates to be removed from the inhalator.
- 15 2. The process of claim 1, wherein the spherical hollow particulates of respirable particle size have an average mass median aerodynamic diameter from about 0.5  $\mu\text{m}$  to about 7.0  $\mu\text{m}$ .
- 20 3. The process of any of claims 1 or 2, wherein the spherical, hollow particulates of respirable particle size have an average mass median aerodynamic diameter from about 1  $\mu\text{m}$  to about 4.5  $\mu\text{m}$ .
4. The process of any of claims 1, 2 or 3 wherein the spherical hollow particulates of respirable particle size have more than about 50% thereof with a mass median aerodynamic diameter less than about 6  $\mu\text{m}$ .

5. The process of any of claims 1 through 4, wherein the spherical hollow particulates of respirable particle size have more than about 70% thereof with a mass median aerodynamic diameter less than about 6  $\mu\text{m}$ .

5      6. The process of any of claims 1 through 5, wherein the medicament is selected from the group consisting of albuterol, amiloride, terbutaline, isoproterenol, metaprotaranol, pirbuterol, salmeterol, fluticasone propionate, budesonide, beclomethasone dipropionate, disodium cromoglycate, bambuterol, mometasone, insulin, and triacetone, and pharmaceutically acceptable salts thereof.

10

7. The process of any of claims 1 through 6, wherein the medicament further includes therewith an excipient selected from the group consisting of polysaccharides, amino acids, lactose, glucose, mannitol, maltodextrins, calcium carbonate, sodium chloride, and combinations thereof.

15

8. The process of any of claims 1 through 7, wherein the medicament is formulated as a dry powdered medicament and the inhalator device is a dry powder inhalator device including a medicament carrier adapted for holding at least one dose of dry powdered medicament, and the providing in step (a) and the activating in step (b) comprise:

20

(a) providing a carrier in a dry powder inhalator in which the carrier is loaded with at least one dose of dry powdered medicament particles comprising spherical, hollow, medicament particulates of respirable particle size suitable for deposition in a human being's lungs, and

25

(b)providing an air flow to the carrier to entrain and to cause initial disaggregation of the spherical hollow medicament particulates and to remove them from the carrier.

5 9. The process of any of claims 1 through 8, further including the step of (c) depositing the removed spherical hollow medicament particulates into a human being's lungs.

10 10. The process of claim 1, wherein the medicament is formulated in a suspension and the inhalator is a pressurized aerosol container, wherein the container has a dispersing valve and is adapted for containing the suspension of medicament, and the providing in step (a) and the activating in step (b) comprise:

15 (a)providing a pressurized, aerosol container having a valve and containing therein a suspension of (i) at least one dose of spherical hollow medicament particulates of respirable particle size suitable for deposition in a human being's lungs, and (ii) a propellant, and

20 (b)activating the valve of the pressurized aerosol container to cause the suspension of spherical hollow medicament particulates to be removed from the pressurized aerosol container.

25 11. The process of claim 10, wherein the propellant is selected from the group consisting of a chlorofluorocarbon, an environmentally safe propellant, and combinations thereof.

12. The process of any of claims 10 or 11, wherein the propellant is an environmentally safe propellant selected from the group consisting of perfluoroethane, 1,1,-difluoroethane, monochlorodifluoromethane, 1,1,1,2-tetrafluoroethane, and combinations thereof.

5

13. The process of any of claims 10 through 12, further including (i) the aerosol container containing therein a suspending agent and (ii) the spherical hollow medicament particulates being in a suspension with the suspending agent.

10

14. The process of claim 13, wherein the suspending agent is selected from the group consisting of oleic acid, partial esters of common fatty acids and hexitol anhydrides, lecithin, and combinations thereof.

15

15. The process of any one of claims 10 to 14, wherein the medicament particulates and the propellant have substantially the same geometric density.

20

16. An inhalator device comprising an inhalator which contains at least one dose of medicament particles comprising spherical hollow particulates that are of respirable particle size suitable for deposition in a human being's lungs.

17. The inhalator device of claim 16, wherein the spherical hollow particulates of respirable particle size have an average mass median aerodynamic diameter from about 0.5  $\mu\text{m}$  to about 7.0  $\mu\text{m}$ .

18. The inhalator device of claim 16 or 17, wherein the spherical hollow particulates of respirable particle size have an mass median aerodynamic diameter from about 1  $\mu\text{m}$  to about 4.5  $\mu\text{m}$ .

5 19. The inhalator device of any of claims 16 through 19, wherein the spherical hollow particulates of respirable particle size have more than about 50% thereof with a mass median aerodynamic diameter less than about 6  $\mu\text{m}$ .

10 20. The inhalator device of any of claims 16 through 19, wherein the spherical hollow particulates of respirable particle size have more than about 70% thereof with a mass median aerodynamic diameter less than about 6  $\mu\text{m}$ .

15 21. The inhalator device of any of claims 16 through 20, wherein the medicament is selected from the group consisting of albuterol, amiloride, terbutaline, isoproterenol, metaproteranol, pirbuterol, salmeterol, fluticasone propionate, budesonide, beclomethasone dipropionate, disodium cromoglycate, bambuterol, mometasone, insulin, and triacetone, and pharmaceutically acceptable salts thereof.

20 22. The inhalator device of any of claims 16 through 21, wherein the medicament further includes therewith an excipient selected from the group consisting of polysaccharides, amino acids, lactose, glucose, mannitol, maltodextrins, calcium carbonate, sodium chloride, and combinations thereof.

25 23. The inhalator device of any of claims 16 through 22, wherein the inhalator comprises a dry powder inhalator including a medicament carrier adapted for holding at

least one dose of medicament and the spherical hollow medicament particulates are in a dry powder form and loaded in the carrier.

24. The inhalator device of any of claims 16 through 21, wherein the inhalator  
5 comprises a pressurized aerosol container having a dispersing valve and being adapted for containing at least one dose of medicament and the spherical hollow medicament particulates are in a suspension form with a propellant and the pressurized aerosol container contains therein the suspension.

10 25. The inhalator device of claim 24, wherein the propellant is selected from the group consisting of a chlorofluorocarbon, an environmentally safe propellant, and combinations thereof.

15 26. The inhalator device of claim 25, wherein the propellant is an environmentally safe propellant selected from the group consisting of perfluoroethane, 1,1,-difluoroethane, monochlorodifluoromethane, 1,1,1,2-tetrafluoroethane, and combinations thereof.

20 27. The inhalator device of any of claims 24 through 26, wherein the pressurized aerosol container further contains therein a suspending agent and wherein the spherical hollow medicament particulates are in a suspension with the suspending agent.

25 28. The inhalator device of claims 27, wherein the suspending agent is selected from the group consisting of oleic acid, partial esters of common fatty acids and hexitol anhydrides, lecithin, and combinations thereof.



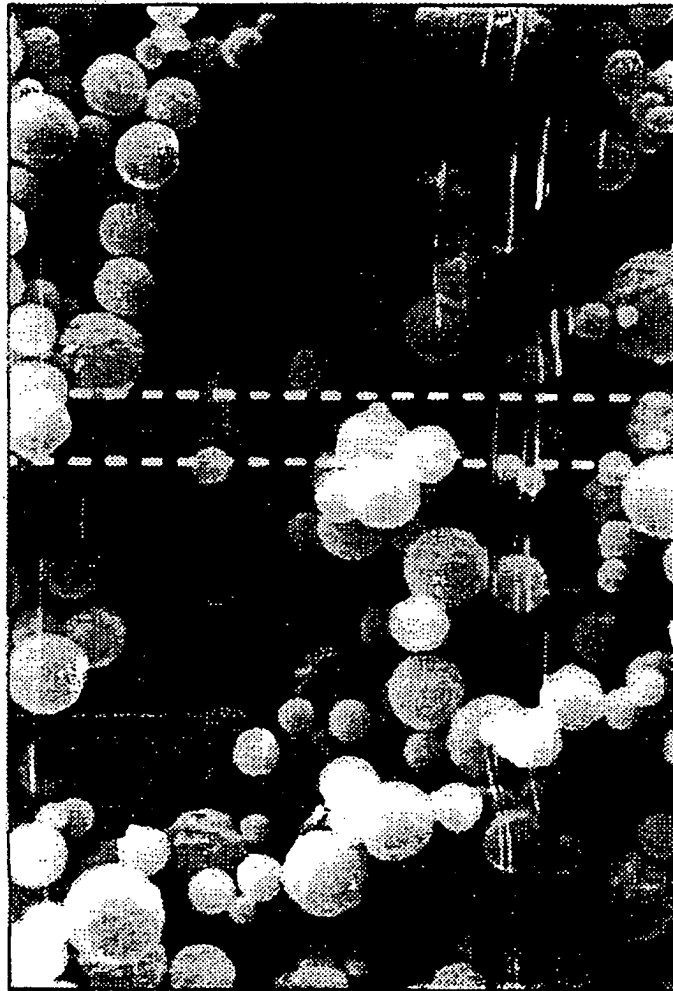
29. The inhalator device of any of claims 24 through 28, wherein the medicament particulates and the propellant have substantially the same geometric density.

5 30. The inhalator device of any of claims 16 through 21, wherein the inhalator comprises a dry powder inhalator containing at least one dose of pure medicament formed of spherical hollow medicament particulates in dry powder form.

10 31. A formulation for a metered dose inhalator comprising a suspension consisting essentially of spherical hollow medicament particulates of respirable size and 1,1,1,2-tetrafluoroethane.

15 32. A formulation for a metered dose inhalator comprising a suspension of spherical hollow medicament particulates of respirable size, 1,1,1,2-tetrafluoroethane, oleic acid and sufficient ethanol to solubilize the oleic acid.

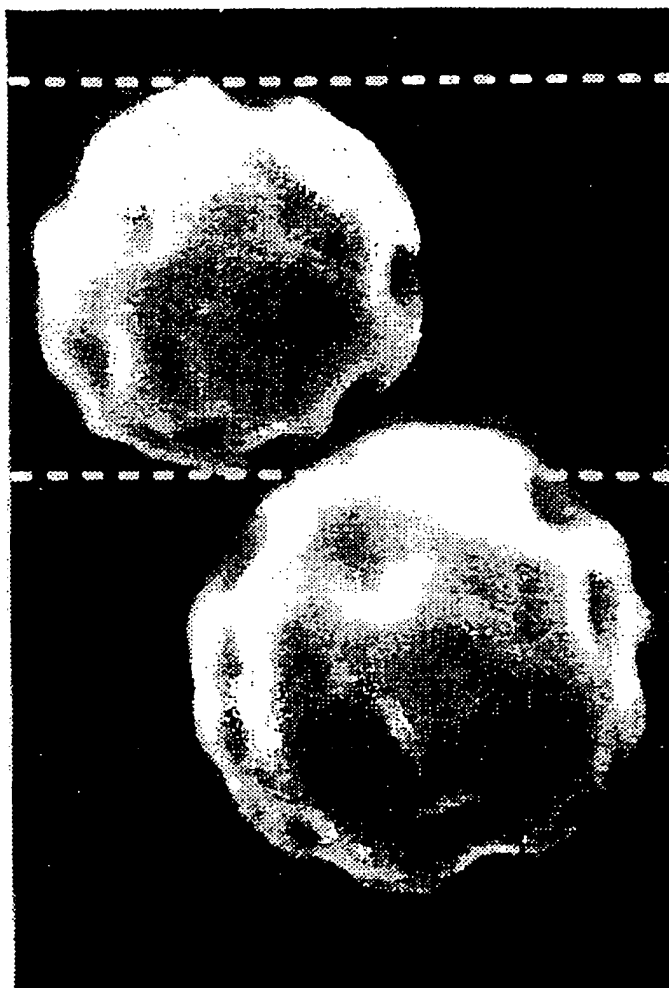
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5 μm

FIG. 1

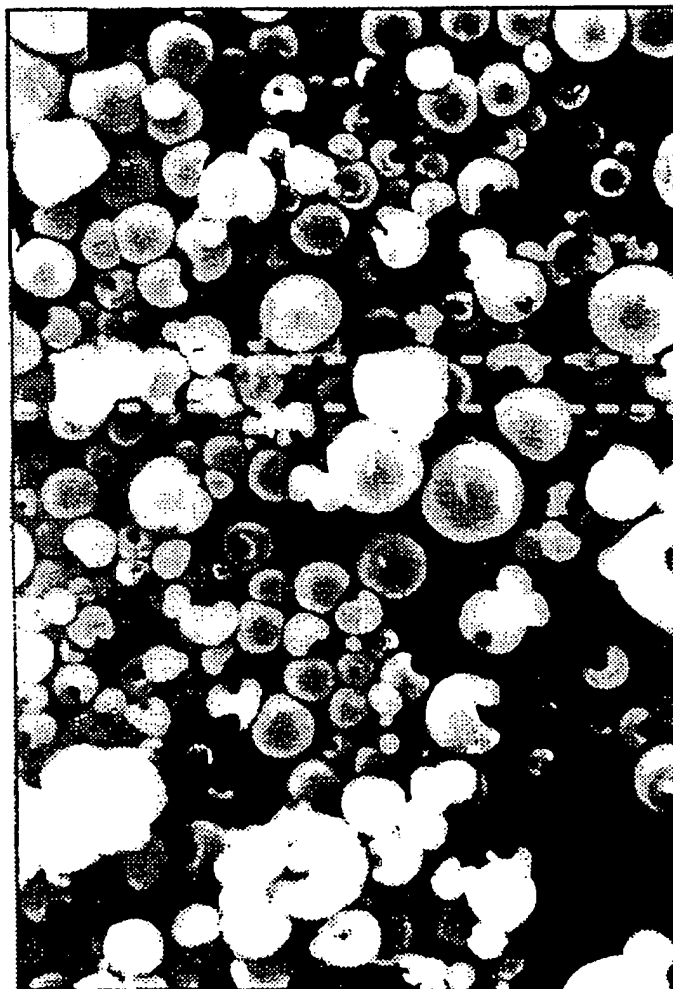
2/7



500 nm

FIG. 2

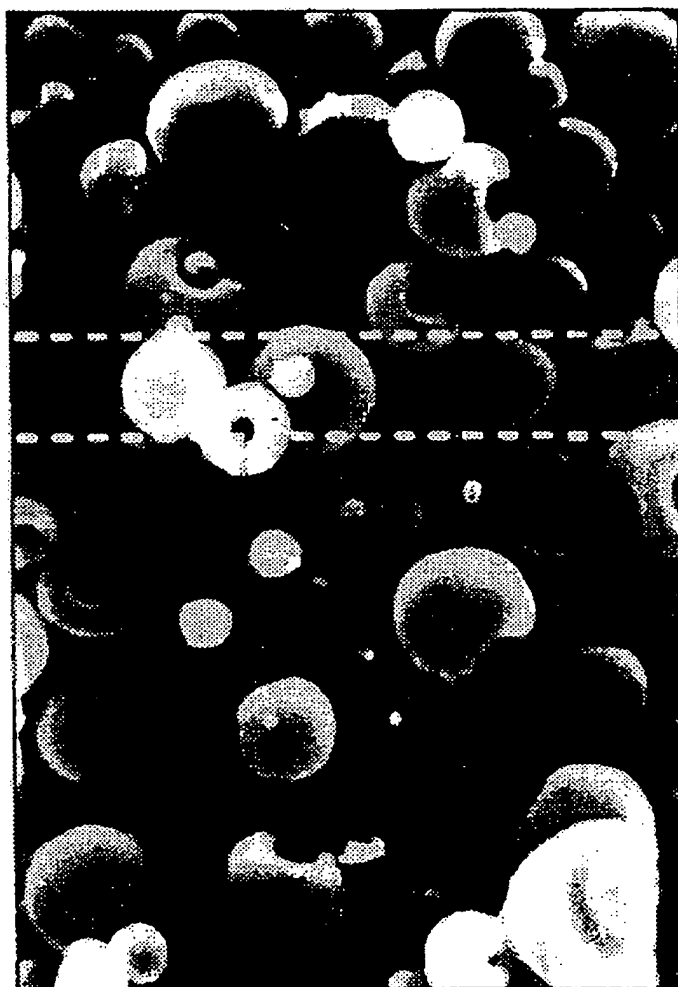
3/7



5  $\mu$ m

FIG. 3

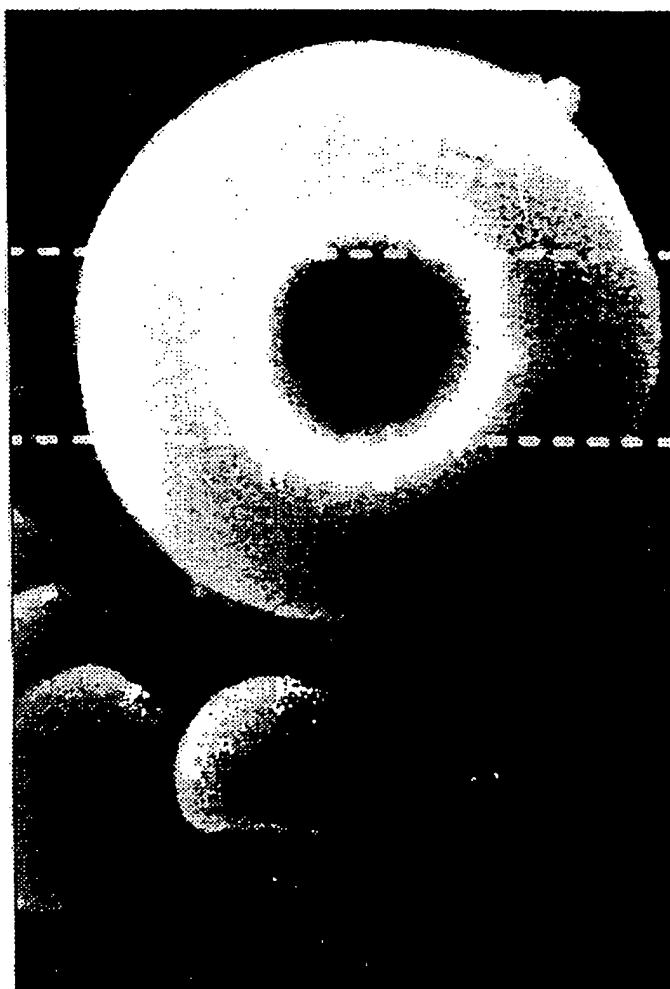
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2  $\mu$ m

FIG. 4

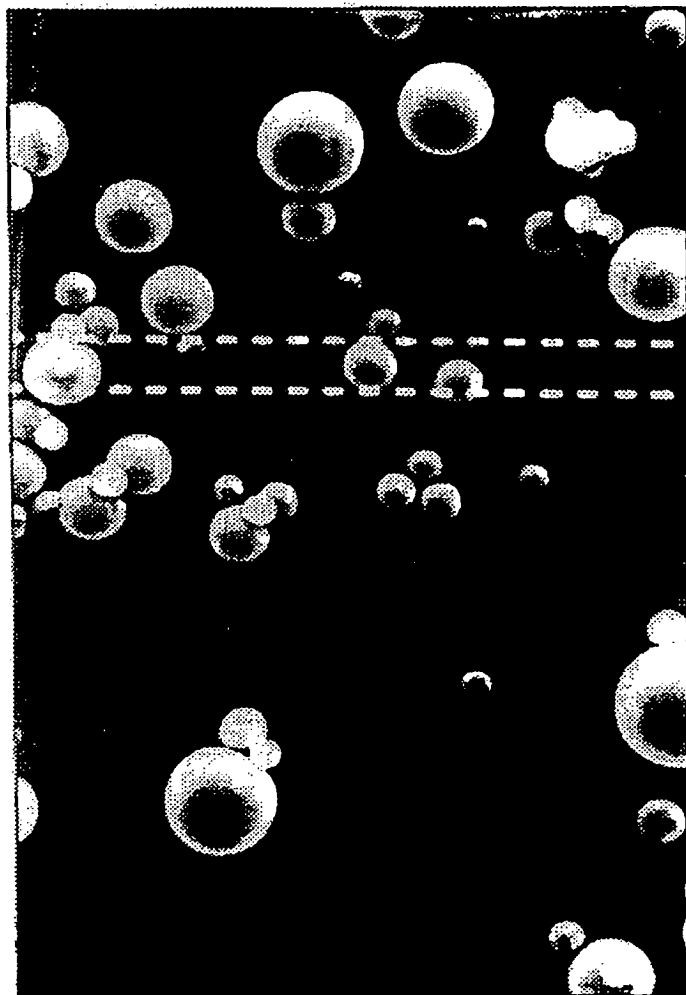
5/7



500 nm

FIG. 5

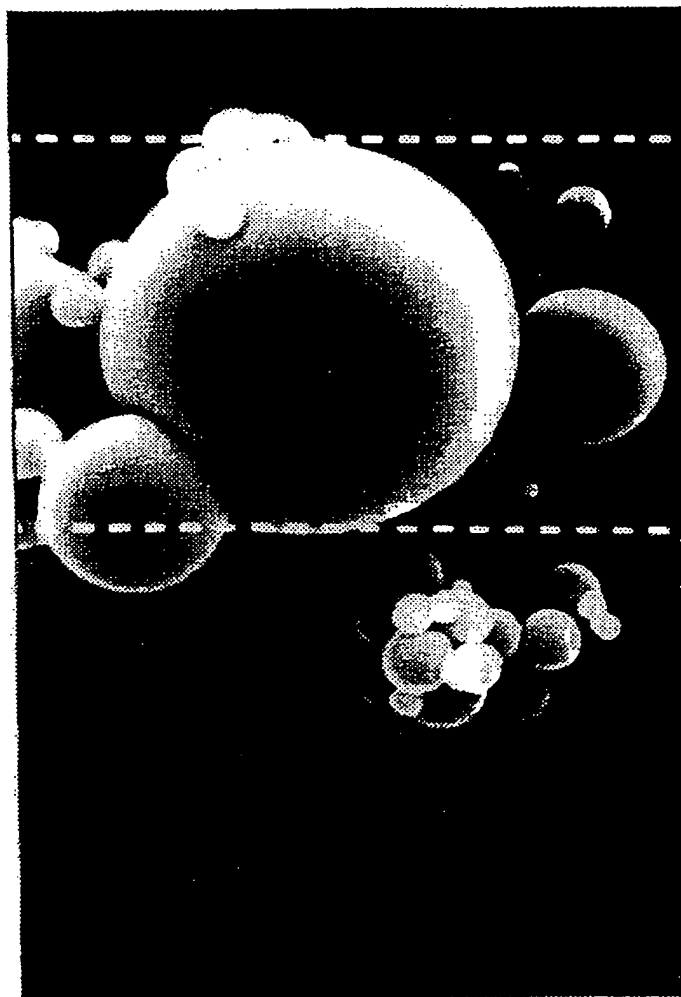
6/7



5 μm

FIG. 6

7/7



5  $\mu$ m

FIG. 7



## INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/EP 97/01560

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 072 046 A (FISONS) 16 February 1983 cited in the application see figures 3-10 see claims 1-3 see page 5, line 12 - line 18 see page 10, line 12 - line 16 see page 19, line 23 - page 20, line 18 ---	1-11, 16-25, 30
P, X	WO 96 09814 A (ANDARIS) 4 April 1996  see claims 2-4 see page 1, line 27 - line 29 see page 7, line 1 - line 9 see page 8, line 35 - page 9, line 2 see page 10, line 24 - line 37 see page 12, line 25 - page 13, line 11 -----	1-9, 16-23, 30

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

28 August 1997

Date of mailing of the international search report

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int:      nal Application No

PCT/EP 97/01560

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 72046      A	16-02-83	AU 540826 B	06-12-84
		AU 8635582 A	10-02-83
		BE 893912 A	24-01-83
		CA 1187415 A	21-05-85
		CH 657273 A	29-08-86
		FR 2510405 A	04-02-83
		GB 2105189 A,B	23-03-83
		HK 10088 A	12-02-88
		JP 4068285 B	02-11-92
		JP 58059914 A	09-04-83
		LU 84291 A	07-02-83
		US 4590206 A	20-05-86
		US 5260306 A	09-11-93
-----			
WO 9609814      A	04-04-96	AU 3530295 A	19-04-96
		CA 2199954 A	04-04-96
		EP 0783298 A	16-07-97
		FI 971332 A	01-04-97
		NO 971438 A	26-03-97
-----			